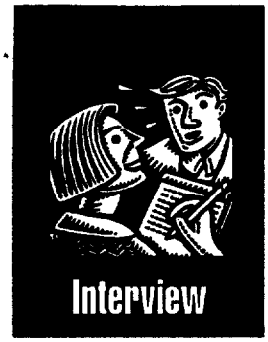


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# Maclyn McCarty

ISTVÁN HARGITTAI

*Maclyn McCarty (b. 1911) is Professor Emeritus at Rockefeller University in New York City. He graduated with an A.B. in biochemistry from Stanford University in 1933 and with an M.D. from Johns Hopkins University in 1937. He worked with Oswald T. Avery (1877–1955) in the early 1940s on the transforming principle. Their research culminated in the publication of the paper by O. T. Avery, C. M. MacLeod, and M. McCarty, "Studies of the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types,"* Journal of Experimental Medicine *1944, 79, 137–158. This work showed for the first time that DNA is the genetic material. Dr. McCarty published a book about the research leading to the discovery,* The Transforming Principle: Discovering That Genes Are Made of DNA *[W.W. Norton & Co.: New York, 1985]. In his subsequent career at Rockefeller, from which he retired in 1981, Dr. McCarty was involved in research on C-reactive protein, the biology and immunochemistry of streptococci, and the nature of rheumatic fever. Dr. McCarty is a member of, among others, the National Academy of Sciences and the American Academy of Arts and Sciences. His many honors include the Robert Koch Gold Medal, the Wolf Prize, and the Albert Lasker Special Public Health Award. Our conversation was recorded in Dr. McCarty's office at Rockefeller University on March 11, 1997.*

**ISTVÁN HARGITTAI (IH):** Just a few days ago, the world learned about the sheep cloning in Scotland. Would you care to comment on it?

**MACLYN MCCARTY (MM):** I don't have the concerns that people have about it, nor do I feel terribly surprised. They had to solve a technical problem to achieve it. It was getting the nucleus from the donor into the ovum under the right conditions so that it would go through the process of ordinary development. They failed in any number of attempts, and only one came through. You can see that there are still uncertainties about it. It was perfectly reasonable to try it, and therefore I am not overwhelmed.

**IH:** Do you consider it a direct continuation of your work?

**MM:** In a sense. There is an awful lot of what you call "direct continuation," because there was no knowledge of what genes are made of at the time we published our work. The whole story of the DNA development has come about since then. It was dependent primarily on knowing what you're dealing with, knowing that it is DNA that is carrying genetic information.

**IH:** *Time* magazine portrayed Watson and Crick as the ones who introduced DNA into science.

**MM:** This is not uncommon. What Watson and Crick did, of course, was come up with the structure of DNA, which involved important implications about its functions. It had a profound impact, but it is unlikely that they would even have done the structural work without our evidence on the genetic role for DNA. It depended on knowing that first, and everything that has happened since all comes from that. I consider the Watson–Crick paper one of the major steps after our discovery, almost 10 years later. But a lot of things had been done in the intervening period to enhance the evidence we had that DNA was the genetic material.

**IH:** Was there any single important step?

**MM:** Rollin Hotchkiss, for example, worked with Avery until Avery retired and continued afterwards. Our experiments had dealt with one character, and that was the organism's polysaccharide capsule. Hotchkiss looked at several other characters. Thus, he showed that two kinds of antibiotic resistance could be transferred with DNA. He also worked with an enzyme and showed that DNA from a cell that had it could transfer it to one that did not have it. This work broadened the base of the evidence pointing to the general validity of our discovery. In the system of pneumococcal transformation, you could transfer any number of traits with DNA.

**IH:** How do you assess the contribution that Erwin Chargaff made between your discovery and the elucidation of the double-helix structure?

**MM:** His work began fairly early after our paper. He was one of the minority who believed its conclusion at the outset and was motivated to change his line of work to a study of the composition of DNAs from various sources. DNAs had been considered so simple and uniform in composition that they could not have the specificity

*Maclyn McCarty in 1982, at the time of his writing the book* The Transforming Principle: Discovering That Genes Are Made of DNA *[W.W. Norton & Co.: New York, 1985]. (Photograph courtesy of Dr. McCarty.)*

*Maclyn McCarty during the conversation. (Photo by I. Hargittai.)*

required for gene function. Chargaff showed that they were certainly not all alike, but varied widely in base composition, and the demonstration of base pairing was very useful to Watson and Crick in their structural studies.

**IH:** Did you have any direct interaction with him?

**MM:** No. It's possible that he talked to Avery, but I don't believe that we knew what he was doing until his first publication on the subject. He has always acknowledged that it was our paper that led to his doing that work. Then when we recently celebrated the 50th anniversary of our discovery, he participated in the affair, and we had a chat at that time. He has always expressed himself negatively about Watson and Crick.

**IH:** What was the most important discovery that your work was building upon?

**MM:** It all started with work on pneumonia. It was Fred Griffith in London who had received numerous sputum samples from patients with pneumonia for bacteriologic diagnosis, and he had become interested in the fact that many of the samples from patients contained four or five different pneumococcal types. Each of these would have a different capsular polysaccharide. He didn't think it was likely that patients had acquired four or five different types and entertained the idea that some interchange of type was going on in the living individual. He set up experiments that were actually designed to look at this in the mouse. He heat-killed pneumococci of one type and put them into the mouse with a small inoculum of living pneumococci that came from a different type but lacked a capsule. When the mouse died, the organisms recovered had the polysaccharide capsule of the killed pneumococci. He followed this up with a number of such experiments and reported the results as the transformation of pneumococcal types. He assumed that the heat-killed cells were releasing something that would stimulate this result. He did not think about it genetically, at least he did not say so. He thought about it as something that came from the heat-killed cells that the living cell used to make the new polysaccharide. This was in 1928, and this was the beginning.

Griffith's experiments were repeated in a couple of laboratories, one of them in Germany, at the Koch Institute in Berlin. Here, in Avery's laboratory, Martin Dawson also repeated the work. It was clear to everybody that it was not the survival of the heat-killed cells but that something else was going on. Dawson then succeeded in getting transformation to work in the test tube, without the use of the mouse.

The next person to work on this problem in Avery's laboratory was Lionel Alloway, who showed that transformation could be achieved using cell-free extracts rather than heat-killed cells. His work was published in two papers in 1933 and 1934, and, from that time, one had the material that made it possible to find out what the active transforming substance was. It was not easy, however.

Colin MacLeod started working with Avery in 1934. He struggled with it for three years, making some progress. It was a difficult system, and he had to give it up because he had no publications from his laboratory work after three years. Another difficulty was Avery's illness which kept him away from the laboratory for a considerable time.

In the meantime, the point of view about the work had changed. Initially, the interest was in pneumonia and its control. The capsule had been shown to be very important in the disease. Pneumococcal cells without a capsule were rapidly ingested and killed by white blood cells and thus did not cause disease. Initially, there was some thought that transformation experiments might help in finding out how the capsule was being synthesized and provide information that would be useful in devising means for control of pneumonia. But as they worked with the transformation system, MacLeod and Avery began to think about what was going on, that is, about the change in the living cell. They found that when they took the cells that had been transformed and now made a capsule that they had never made before, the active transforming material was reduplicated in the cell in addition to the continued production of the new capsule. This comes close to the definition of a gene. This gradual recognition really determined Avery's drive to find

*Oswald T. Avery. (Photograph courtesy of Dr. McCarty.)*

out what the stuff was.

MacLeod did other things in the lab from 1937 to 1940, and he and Avery agreed to get back to the job in the fall of 1940. In the course of this renewed effort, MacLeod was offered the position of Chairman of the Department of Microbiology at New York University (NYU) Medical School. He was told that he better take it, because there was no opening for him at Rockefeller, since a replacement for Avery, who was soon to reach emeritus status, had already been selected. He left in July 1941. That year I was working at NYU with a former Avery person, William S. Tillett. Tillett had been at Rockefeller for eight years in the 1930s. He helped get Avery to accept me in his laboratory on a National Research Council fellowship that I had just been awarded. This is how I came here in 1941, right after MacLeod had left.

Avery was 64, and the retirement age was 65. He became emeritus at 65 but stayed on. He was dependent on somebody being with him. It didn't take long for me to start working with him, and I picked up where MacLeod had left off, continuing to pursue the nature of the substance that was in these extracts.

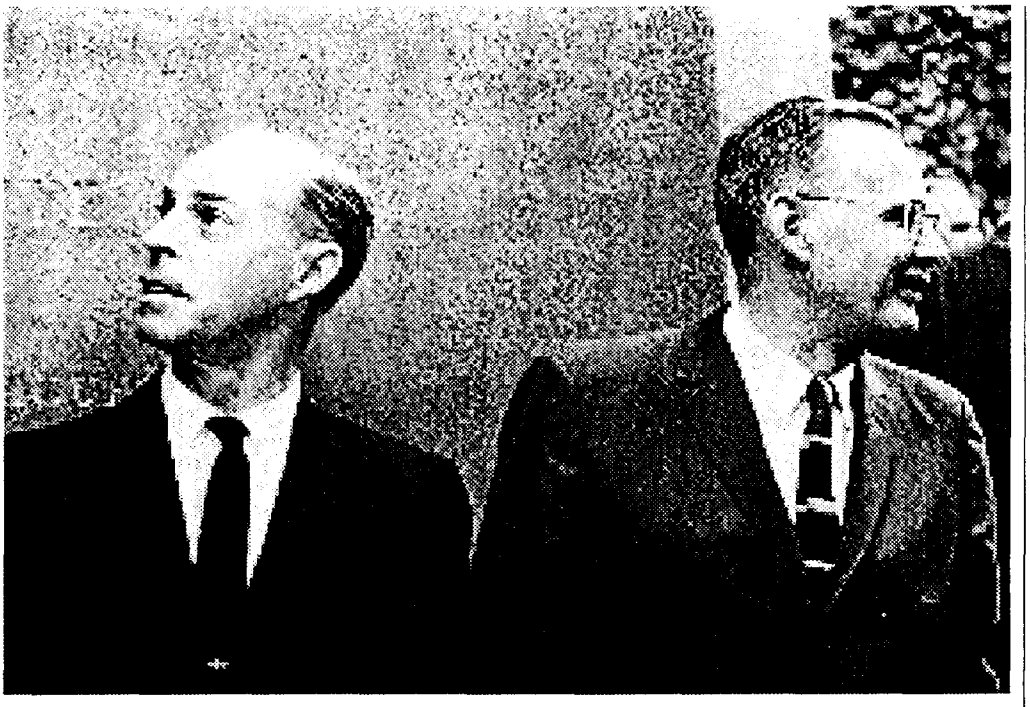
**IH:** Could you then summarize the work from 1941 on, resulting in the 1944 publication?

**MM:** Let me say first that what MacLeod had done earlier was very important. For example, you could take these extracts and deproteinize them by shaking with chloroform, a method for deproteinizing biological materials that had been worked out years earlier. Many other things had also been established. The first recognition that DNA was a constituent of the extracts had come in January 1941. This was kept in mind during the subsequent work, but reproducible fractionation procedures proved difficult to devise. In June 1941, MacLeod was writing up the status of the experiments prior to his departure. He indicated that maybe if you got rid of the polysaccharide, which was there in fairly large amounts, you would eliminate the activity. This was not because they thought that the polysaccharide was the transforming substance but because it might have to be present as a template to initiate the synthesis of new polysaccharide.

In the Avery lab, they had a soil bacillus that produced an enzyme that would split the polysaccharide of type III, which was the type being used in the experiments. My first task was to completely eliminate the polysaccharide from an extract, using this enzyme, to see what would happen. The obvious result was that it made no difference; the transforming activity was not affected by getting rid of the polysaccharide. That made us realize that we ought to get rid of it in order to purify the product. When we did this and treated the extract with alcohol, there was still a large amount of fibrous precipitate, which had been attributed to polysaccharide. This turned out to be DNA. So we began focusing more on DNA, and the next experiments that supported the possibility of its importance were carried out with the ultracentrifuge.

We found that the active material in these extracts was of high molecular weight. It would deposit rapidly in the lower part of the centrifuge chamber. We were testing the material both chemically and for transformation, and the evidence was mounting that the only component that concentrated with this high-molecular-weight fraction was DNA. We did other experiments, such as electrophoresis, and the behavior of the material was again fully consistent with the notion that the active substance was DNA. The focus of our work then shifted to getting a fraction free of other detectable components and containing only DNA.

Although MacLeod was at NYU at the time, he kept his interest in the work. He came back early on to teach me the handling of large amounts of bacteria. We grew organisms in hundreds of liters of medium and prepared several lots of relatively pure substance with elementary analysis consistent with DNA and little evidence for contamination with protein or other substances by a variety of tests. This is how we finally came to our conclusion in the spring of 1943 and started working on the publication. Avery, at his customary summer retreat in Maine, worked on the Introduction and Discussion and put together the experimental part, going back to the early work of MacLeod as well as my own.



*Colin M. MacLeod (1909–1972) on the left and Maclyn McCarty at the dedication of the Avery Memorial Gate in 1965. (Photograph courtesy of Dr. McCarty.)*

We finished the manuscript in the fall and got it to the editor of the *Journal of Experimental Medicine* in November 1943.

**IH:** Coming back to your experiments and handling large amounts of bacteria, were there safety precautions?

**MM:** Indeed there were. If you had a fine mist coming out of the centrifuge, you had bugs all over the place. A technician in the lab developed a protecting housing around the centrifuge, and steam was used for sterilization before opening the housing. Then we handled all of the materials with towels soaked in a germicidal solution and heat-killed the bacteria at 65°C for 30 minutes as soon as they had been removed from the centrifuge cylinder and placed in suspension in salt solution. After that, we didn't have to worry about infectivity.

**IH:** Apart from the initial interest in pneumonia, would bacteria have been the most convenient subject to study in any case?

**MM:** The key is not the bacteria, the key is the phenomenon of transformation, which just happened to be in bacteria. It was the first model providing a test for genetic activity. The geneticists of those days worked with various techniques, but none of their procedures would lead to a test of the chemistry of the process. The final recognition that transformation was possibly a model for genetic transfer is the point. There wasn't any model before.

**IH:** When you determined that DNA was the transforming principle, was it assumed that it had universal validity?

**MM:** The reason that you would at least assume the possibility that it was universal was because it was already known that the chromosome is where the DNA is. This suggested right away that this was a possibility.

**IH:** Didn't you feel an urge to go on with this research?

**MM:** That's the question that I have thought a fair amount about. The activities that we were engaged in were different from what was needed next. I was an MD, as were Avery and MacLeod, and I had gone to medical school with the intention of doing disease-related medical research. And this is what I had done before, and this is what the Avery laboratory was about as well. I continued working with Avery until 1946, that is, two years after our 1944 paper. We worked to substantiate the idea that we were dealing with DNA; for example, I isolated a purified DNase and demonstrated that it was highly potent in destroying the activity of transforming DNA. We thought about next steps, what variation between nucleic acids must depend on. And I think it is just as well that I did not continue in this direction. None of my training was in the direction of structural work. Then, in early 1946, I got an offer to take over the laboratory for streptococcal infection and rheumatic fever at Rockefeller. I was trained as a pediatrician and had seen a lot of rheumatic fever, and we knew that it was somehow related to streptococcal infection, but we didn't know how. So here was a problem that certainly was up the alley of what I wanted to do, plus the fact that it would give me a permanent position. From then on, I closely followed what was going on in DNA research without getting involved in it again. And this is probably just as well.

**IH:** Is it correct to say that the main opponent to accepting your discovery was Alfred Mirsky of The Rockefeller Institute?

**MM:** Yes. He took the view that you really couldn't tell whether you had as much as 1% protein in the DNA preps. That would have been millions of molecules. I don't know what motivated him, but he was very vocal about this. His opposition was well known in the biochemical community and in the cell biology community.

He was working in a laboratory two floors above us. He had gotten the nucleoprotein from mammalian cells by a very nice technique. Nucleoprotein is soluble in 1M salt solution. If you bring the salt concentration down to the usual 0.14 M, it all precipitates out. He could purify it from other things this

*Maclyn McCarty with James D. Watson and Francis H.C. Crick in La Jolla, California, in 1977, at the time Dr. McCarty was given the First Waterford Biomedical Award (the vase in front of him). (Photograph courtesy of Dr. McCarty; by Robert Smull—The Lensman Photography, 1965 Fifth Avenue, San Diego, CA 92101.)*

way. He thought he could extract our pneumococci with salt. It turned out that very little stuff was extracted. We had worked together on an experiment, in which we took one of our large batches and went through the salt procedure. We got a little bit of this fibrous precipitate on bringing the salt concentration down. I tested it, having some trouble putting it into the solution, but it was active in transformation. However, in some way or other, Mirsky thought that this experiment was an important step in our process, because he wrote some time later that it had led us to wash our cells thoroughly before we would proceed with extraction. But this was not the case as I had been prewashing the cells for a couple of years, since we first realized that we didn't need the polysaccharide; we washed the cells to get rid of it before we tried to get rid of the remainder with an enzyme. So this was a misinterpretation on his part, and he thought we were ignoring his contribution, which was really that one experimental collaboration. He had also provided us with some of his pure mammalian DNA, which was helpful. Actually, I had the idea of reporting the experiment with Mirsky in the paper, but Avery vetoed it. Mirsky was widely enough known, and vocal enough, and influenced a lot of people. It took him a long time to come around. About 25 years later, he wrote an article in *Scientific American* in which he cited our work with pneumococcus, and in this article he seemed to accept our findings of 1944. Thus he knew it later.

**IH:** Did he ever say he was sorry?

**MM:** No, never.

**IH:** In a book about Nobel and the Nobel Prize [*Nobel: The Man & His Prizes*, 3rd ed.; The Nobel Foundation and W. Odelberg, Eds.; Elsevier: New York, 1972; p 201], it is said "it is to be regretted" that the discovery of DNA being the transforming principle was not awarded the Nobel Prize. This is quite an unusual and unique statement. Did the discovery belong to chemistry or to physiology or medicine?

**MM:** I think because of the biological activity involved in it, it's more likely to have been in physiology or medicine. It's hard to say, though, because biochemical fractionation played a major role in it.

**IH:** Let's get back to your own history.

**MM:** I was born in 1911 in Indiana. When I was growing up, we were moving around because my father was in the automobile business. I was in Portland, Oregon, for a while and started school there, then went back to Indiana, and finally to Wisconsin. I went to Stanford University for undergraduate studies and got my degree in biochemistry. I went to medical school at Johns Hopkins because I thought that it was where you went if you wanted to do medical research. I specialized in pediatrics and started doing research in infectious diseases. But it was always my intention to get into the laboratory when I had finished my practical training. This is what I did when I got to New York.

**IH:** How did you become interested in chemistry?

**MM:** Four of us in our high school set up chemical laboratories in our basements. We had a club, "Amateur Chemists." This was in Kenosha, Wisconsin. Only one other of the four of us went into science. My mother told me that by the time I was 10, I told her I was going into medical research. The chemical aspect was something I was interested in, and so I took the biochemistry training before medical school.

**IH:** Did you read Paul de Kruif's *Microbe Hunters?*

**MM:** I had already made my decision before the book came out, but I read it, and it further stimulated my interest. However, it did not initiate it, and I really don't know what did.

**IH:** Any other interests?

**MM:** I have been interested in history and in science history. When I was putting together my book, I realized that there were a lot of things I didn't really have any solid evidence about.

**IH:** Can you tell us something about Oswald Avery?

**MM:** He was not a very outgoing person. He was a small man who was quite restrained, at least by the time I got to know him. He was a lifelong bachelor. At the time I knew him, he no longer liked to talk in public. We induced him to talk at our regular staff meeting in December 1943. By then, our paper was in press, but he had not talked there for years. He was President of the Society of American Bacteriologists the year that I came to Rockefeller. He gave the Presidential Address, and he would not let it be published. Talks of this kind were not science, and he just didn't want his general comments in print.

**IH:** So he was known as a reserved person, somebody who would not rush to publish.

**MM:** There is no doubt about that.

**IH:** Then shouldn't Dr. Mirsky have had a difficult time convincing people that Avery's publication may have been premature?

**MM:** He was talking to a different group of people, not to bacteriologists. The geneticists and the cell biologists didn't know so much about Avery.

**IH:** Was Avery's reservedness in disseminating the discovery frustrating for you?

**MM:** Obviously there was some frustration, but he was a very likable person and quite revered around here; and everybody looked out for him, particularly since he had been ill. He had hyperthyroidism, a disease in which the thyroid overworks. They had to operate and take out a considerable part of his thyroid gland. He was ill for years, and people were very solicitous about it, including MacLeod. Avery had a tremor, which comes with this illness, and he could not do experimental work anymore, and he got quite depressed at times. He was just recovering fully in the late 1930s.

**IH:** The Rockefeller Institute, later, Rockefeller University, has produced strong lines of research in your area and related areas. Any comment on this?

**MM:** The early leadership was very strong. The hospital started a little later, in 1910, and its first director was Rufus Cole, who selected people like Avery. The leadership of the Institute and the hospital did a very careful job, and the time was also ripe for building up a strong institution.

It all started with John D. Rockefeller, Sr., the man who originally accumulated the fortune. He had an adviser, Frederick Taylor Gates, who had been a Baptist minister. This man read a book on medicine by Sir William Osler in the 1890s. Osler was a Canadian who came down to the U.S. and was involved with the building of the Johns Hopkins Medical School. He had written a famous textbook on medicine. Gates read the book and realized that there were so many instances in medicine where you could only describe the diseases but could do nothing effective about treating them. This is why he persuaded Rockefeller to set up an institute for medical research. It was organized in 1901. It was very strong from the very beginning.

**IH:** Do you anticipate that it will continue to be as strong?

**MM:** Obviously, times have changed. The support for research for the first 50 years came totally from endowments. It was after World War II, in the early 1950s, that federal support began, with the National Institute, later, Institutes, of Health. It was not until the mid-1950s that I had to start thinking about external support. The number of people engaged in biomedical science today is probably between a hundred and a thousand times as many as it was in our early days. At that time, there were very few places where one could go, and Rockefeller was one of those few places. It's an entirely different situation today.

**IH:** Are your children aware of the DNA discovery?

**MM:** My oldest son is 61; he is a physical chemist who worked more in chemical engineering and is now retired. My second son is Head of Biology at Johns Hopkins. My third and much younger son, born in 1958, is named Colin Avery McCarty. I also have a daughter and eight grandchildren. I think they are all aware of the DNA discovery. One of my nieces taught biology, and when this came up in the textbook, she would say, this is my uncle. She got laughed at by her students; they didn't believe her.

**IH:** Did you get recognition, the three of you, for your discovery?

**MM:** Not the three of us—not together. However, I did this work when I was young, and there was the Eli Lilly award in bacteriology and immunology, and Avery nominated me for this prize. The age limit was 35, and I got it just before I turned 35, specifically for the work on the transforming principle. The highest recognition I got was the Wolf Prize, in 1990.

**IH:** You started a whole new career when you were 35. Were there any comparable achievements in your research after the discovery of the transforming principle?

**MM:** Our goal was to discover the mechanism of how streptococcal infection causes rheumatic fever, and it was never reached fully. It has not been reached yet. This goal seems to be much harder to reach than the one in the DNA study. But we did contribute a lot of things to the problem, and our laboratory was recognized for its contributions.